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Hemoglobin E in Northeast India: A review on its origin, distribution, migration and health implication

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ABSTRACT: A systematic review of the studies on hemoglobin E in Northeast India has been carried out to understand the magnitude of research undertaken on this aspect during the last seven decades. Owing to the high prevalence of hemoglobin E in this part of India different authors have studied this hemoglobin from different perspectives and found conflicting results. However a systematic review of such studies is lacking from a holistic point of view. Most of the epidemiological, in vitro as well as in vivo studies show signatures of selection with this hemoglobin locus. However, how this polymorphism is maintained at different rates at different geographical region is still a matter of contention. This review will fill the gap from all perspectives starting from the frequency distribution of hemoglobin E and its spread in different parts of Northeast India, its relationship with malaria hypothesis, the population migration, population affinity and most importantly the health implication arising out of it. A probable origin of hemoglobin E among an Austroasiatic population of Northeast India has been postulated with the help of advance molecular anthropological knowledge like the deep rooted markers of mt DNA and Y-chromosome haplotypes.

KEY WORDS: Hemoglobin E, Northeast India, selection, population affinity, health

Introduction

It has been estimated that more than 70 lakh babies born each year with either a congenital abnormality or with a genetic disease (Christianson et al. 2006). Approximately 25% of these babies suffer from only five disorders of which two belong to inherited disorders of hemoglobin (Weatherall 2010). As such human β-globin gene located on chromosome 11p15.5 is one of the most intensely studied genetic polymorphism of all human loci. The DNA polymorphism present in the hemoglobin cluster is also very interesting and it has also been extensively used to examine human evolutionary history (Das and Talukdar 2001). Mutation of β-globin gene causes β-thallasemia and other hemoglobinopathies of which HbS, HbE, HbD and HbC are most common genetic abnormalities in the world including India. Spatial dis-

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tribution of the deleterious β-globin mutations in Indian population is extremely diverse and certain mutations are restricted to particular population groups only. Various evolutionary forces such as natural selection, mutation, recombination, migration and genetic drift are known to regulate the frequency of these deleterious mutations in human population. Of the various structural hemoglobin variants, HbS (Codon 6A-T) variant is widespread among various tribal populations of India (frequency 0–40.0%) where a small frequency has also been found among the caste populations (Rao, 1998). HbD Punjab (Codon 121 G-C) has an incidence of 2–3% among the Sikh population of Punjab and is also reported among some other population groups of India. On the other hand HbE (Codon 26 G-A) is confined exclusively (frequency 0.4–64.5%) among the people originating from Eastern India, especially Northeast India. It has been argued that the different forms of abnormal hemoglobin originated in different parts of the world due to its different survival advantages and one of such advantages being the endemic malarial condition. Because of conduciveness of abnormal hemoglobin in the malaria endemic areas most of the population groups of Northeast India have been studied during the last few decades either singly or in combination to have the distributional pattern of hemoglobinopathies in different population groups. It is very important to have a sum up of most of the works on hemoglobin E in Northeast India to have its trend of research and to gear up new possibilities of research in this particular domain.

Materials and methods

A search of PUBMED, MEDLINE and EMBASE (1950 to January 2016) databases was supplemented by manual searches of bibliographies of key retrieved articles, reviews of abstracts from scientific meetings, and contact with experts. The search has been carried out taking into consideration few points in mind i.e. peopling of Northeast India, hemoglobin research in Northeast India particularly in different states of Northeast India, origin and spread of hemoglobin E, hemoglobin E and malaria hypothesis, hemoglobin E and health. Further the frequency distribution of this particular hemoglobin variant in different states of Northeast India has been supplemented in different tables.

Peopling of Northeast India

Many researchers veered their attention to Northeast Indian region due to its considerable variation in ethnic and linguistic structure. It is bordered by the Himalayas and the Bay of Bengal in the North and South respectively and it constitutes an exclusively slender passage that connects the Indian subcontinent to East Asia and Southeast Asia. Earlier the entire Northeastern part of India was referred to as Assam but after the Independence of India in 1947 new territories and states were came into being. Now the region is composed of seven administrative units and is the homeland of different ethnic communities with diverse linguistic and sociocultural traditions. In 2002 the state of Sikkim was also included as the eight administrative part of Northeast India. It is said that the diverge population came to this mainland India from different directions and

at different times through various routes like the Northern passage which opens at Bhutan and Tibet, the Eastern route of Assam-Myanmar and from the Western route which constitutes the Ganges and Brahmaputra valley.

The extensive linguistic diversity of Northeast India is represented by three major linguistic families: Austro-Asiatic, Indo-European and Tibeto-Burman. The Austro-Asiatic group has a linguistic relation with the Mon-Khmer people of mainland Burma as well as Thailand and its main representative is the Khasis of Meghalaya. The Khasis practice matriarchy unlike the other tribal population of Northeast India. It is believed that the Indo-European group migrated to this particular land from the West and represented by the Indid Assamese, the major inhabitants of Brahmaputra valley. Tibeto-Burmese populations are the earliest inhabitants of this land. One of the subdivisions of Tibeto-Burman i.e. North-Assam group of languages are spoken by most of the tribes of Arunachal Pradesh as well as Assam and Manipur. Another subdivision known as Assam-Burma group is spoken by the Bodo group of tribes of Assam, Meghalaya and Tripura; Karbis of Assam; Nagas of Nagaland; Mizo-kukis of Mizoram; Meities of Manipur etc. Besides, there is another linguistic group i.e. Siamese-Chinese, which is spoken by a limited number of population groups. Tai which is one of the sub divisions of Siamese Chinese is spoken by Aiton, Turung, Khamti,

Fig. 1. Map of Northeast India showing different regions.

Khamyang and Phakials of Assam and Arunachal Pradesh. Once, Tai was also the original language of the Ahom, a major population group of Assam. A more recent addition to the population of Northeast India is the tribal people of Orissa and Chotonagpur most of which are from the Kolarian linguistic group and were brought to this mainland as workers in the tea gardens of Assam.

Hemoglobin E research in Northeast India

Research on hemoglobin E started in Northeast India when Chatterjea (1959) reported some sporadic cases of HbE in Assamese population. A few years latter Chaudhuri et al. (1962) reported a relatively high percentage of HbE (0.099) among the Totos, a Tibeto-Burman population of Totopara in the Assam-West Bengal border. With these few investigations it became an interesting area of research in Northeast India just within a decade of its discovery (Chernoff et al. 1954; Itano et al. 1954).

Initially a strong relationship between HbE and Austro-Asiatic linguistic groups of Southeast Asia was pointed out by Flatz (1967) and he hypothesized that high frequency of HbE could also be expected in the population groups of Northeast India which have ethnic relation with Southeast Asia. In view of this observed association Das et al. (1971) and later Flatz et al. (1972) veered their concentration towards three population groups. The first one was the Khasis of Meghalaya (an Austro-Asiatic group); the second was that of the Ahom of Assam, a Tai group related to Shan of Burma (Myanmar), who had migrated from Myanmar during 13th century A.D., and an Assamese caste population of Lower Assam as a base for comparison. The first publication (Das et al. 1971) of this study showed a high frequency of HbE (0.2 19) among the Khasi, and a higher frequency (0.359) among the Ahom. The second publication of the survey (Flatz et al. 1972) also validates the earlier findings. The high frequency of the gene among the Khasis was consistent with the hypothesis of a correlation between Austro-Asiatic linguistic affiliations with HbE.

At that time the high prevalence of HbE gene among the Ahom led to much speculation. Since Flatz et al. (1965) did not find HbE genotype among the Thai population from South-West China they argued that it was not likely that the Ahom descended directly from the Thai population of South-West China. On the other hand historical records indicate a process which they interpreted as '*Thaization*' of Austro-Asiatic groups throughout South-East Asia during the early centuries of Thai migration (Wood 1961). The process was evident in the Shan of Burma, who were Thai speakers with considerable prevalence of HbE (Than-Batu and Hla-Pe 1971). It was highlighted that the Ahoms were once a sub division of the Shan, they speculated that it was quite possible that their genetic structure was predominantly Austro-Asiatic inspite of their prevalent culture and language. This relationship explained the high prevalence of HbE among the Ahom. A later work (Das et al. 1975) also confirmed the high frequency of HbE gene among the Ahom population.

The Assamese population, which includes the Caucasoid caste groups including the people from indigenous Muslim community, presented a somewhat lower

but still considerable frequency of HbE gene (Ahmed Das 1994). The sample collected by Flatz et al. (1972) was from Lower Assam and showed a frequency of HbE gene of 0.107, whereas the later work (Das et al. 1975) was from Upper Assam with a little higher frequency of HbE gene (0.135). They suggested that these populations had no doubt acquired the gene from surrounding populations with high frequency of HbE gene. In a later study Flatz et al. (1972) examined five individuals from the Kachari, a Bodo group of tribes belonging to the Tibeto-Burman linguistic family and found that all of them had HbE, either in heterozygous or homozygous condition. This indicated that an appreciable frequency of HbE gene could be found in this group. Therefore in 1975 a large number of individuals belonging to this group were examined. The sample was drawn from rural areas of Upper Assam. It showed frequencies of HbE gene little above 0.50. This observation drew special attention at that time in view of the fact that so far very little or no HbE had been detected in any Tibeto-Burman groups of South-East Asia (Flatz 1967). After that the most significant observation was the finding of high prevalence of HbE in the other Tibeto-Burman speakers including Sonowal Kacharis (0.549), Boro Kacharis (0.645), Garos (0.499), Rabhas (0.535), Lalungs (0.447) and Rajbanshis (0.350), where the percentage of HbAE ranges from 37.0% to 55% and HbEE ranges from 15.0% to 31.0%. At that time the presence of HbE among the Bodo Kacharis was the highest frequency of any abnormal hemoglobin gene so far reported from any population in the world (Deka et al. 1988). Thus a rethinking was made about the high frequency of HbE among the Ahom and it was then suggested that it might be not entirely due to their Austro-Asiatic background. Their ancestors in Burma, the Shans have a lower frequency (0.14) of HbE in comparison to them. The most likely explanation at the time of investigation was that it might be related to the considerable flow of genes from the local Tibeto-Burman population to this population after their migration to Assam 700 years ago. Selection and demographic history were supposed to be equally responsible for alterations in the frequency of a gene like Hb E (Deka et al. 1988).

Mukherjee and Das (1990) suggested that a possible reason for the rise of HbE frequency among the Ahom community might be related to the gene flow from Chutia population (a Bodo group of people) as intermixture of Chutias with the Ahom had been suggested in literature (Chatterjee 1974). Deka et al. (1988) also conducted a study among the Brahmins (a priestly caste) and found that they have a low HbE frequency which was significantly different from that of the other Caucasoid groups of Assam. They suggested that Brahmins being a priestly caste occupy the highest position in the caste hierarchy and it was possible that caste endogamy had been stricter in them in comparison to the castes with lower position in the hierarchical system. That time it was also a matter of query that whether the high frequency of abnormal hemoglobin found in Northeast India was really HbE or other variant with similar electrophoretic mobility (e.g. Hb Agenogi) and the confusion was cleared by H. Lehmann in a study of 13 blood samples from several ethnic groups in Assam collected by Prof. Flatz. They went for fingerprinting of three samples and also electrophoretic studies which proved that the common abnormal hemoglo-

Table 1. Hb E frequency distribution in several population groups (Mongoloid origin) of Assam, Northeast India

Sl. No.	Population from Assam	N	HbAE %	HbEE %	HbE frequency	Source
			Linguistic group Kam-Tai			
1.	Ahom	82	45.1	13.4	0.359	Das et al. 1971
2.	Ahom	129	46.5	11.6	0.349	Flatz et al. 1972
3.	Ahom (Sibsagar)	89	41.6	5.6	0.264	Das et al. 1975
4.	Ahom (Dibrugarh)	181	46.4	11.1	0.343	Das et al. 1975
5.	Ahom	119	47.1	16.8	0.403	Deka et al. 1988
6.	Ahom	125	41.6	10.4	0.304	Balgir 1991a
7.	Ahom	238	--	--	0.414	Das and Sengupta 2013
			Linguistic group Tibeto-Burman			
8.	Boro Kachari	131	47.3	31.3	0.549	Das et al. 1980
9.	Boro Kachari	110	38.2	45.4	0.645	Deka et al. 1988
10.	Chutiya	62	46.8	6.4	0.298	Deka et al. 1988
11.	Garo	135	37	31.1	0.499	Das et al. 1980
12.	Mikir	131	27.5	6.1	0.198	Das et al. 1980
13.	Mishing	25	32	44	0.600	Deka et al. 1988
14.	Mishing	318	49	22.6	0.462	Das and Sengupta 2013
15.	Mishing	52	--	--	0.403	Sharma and Mahanta 2009
16.	Karbi	110	29.1	8.2	0.227	Deka et al. 1988
17.	Lalung (Tiwa)	114	50.4	19.3	0.447	Das et al. 1980
18.	Mech-Kachari	124	44.4	31.5	0.536	Balgir 1992
19.	Rabha	128	55.5	25.8	0.535	Das and Deka 1980
20.	Rajbanshi (A)	46	43.5	23.9	0.456	Das and Deka 1980
21.	Rajbanshi (B)	46	52.1	17.4	0.434	Das and Deka 1980
22.	Rajbanshi (C)	72	29.2	8.3	0.229	Das and Deka 1980
23.	Rajbanshi (Total)	164	39.6	15.2	0.350	Das and Deka 1980
24.	Rajbanshi	102	36.3	4.9	0.230	Deka et al. 1988
25.	Sonowal Kachari (Upper Assam)	555	49.7	26.1	0.509	Das et al. 1975
26.	Sonowal Kachari (Lower Assam)	131	47.3	31.3	0.549	Das and Deka 1980
27.	Sonowal Kachari	106	45.3	17	0.396	Deka et al. 1988
28.	Sonowal Kachari	158	50	31.6	0.562	Balgir 1993
29.	Sonowal Kachari	112	45.5	31.1	0.549	Barua and Kotal 2008
30.	Tiwa	27	25.9	18.5	0.315	Balgir 1995
31.	Toto (Assam-Bengal border)	116	19.8	0	0.099	Choudhuri et al. 1962
32.	Totos (Assam Bengal Border)	443	49.21	19.19	0.438	Bhattacharyaa et al. 2013
33.	Sut	22	4.6	0	0.023	Balgir 1995

bin in Northeast India was actually HbE (Deka et al. 1987). Several small scale studies in the latter period found that the frequency of HbE ranges from 0.000 to 0.640 in various populations of Mongoloid origin whereas it is between 0.028 to 0.300 among the populations of Caucasoid origin in Assam and its neighbouring states (Tables 1–7).

There were several attempts to review the distribution pattern of HbE in several population of Northeast India (Das and Deka 1980; Mukherjee and Das 1990; Saha 1990; Das 1991; Bhasin et al. 1994; Balgir 2005) and this is an addition to the earlier studies. Within the Mongoloid populations no HbE has been reported among the rural Naga tribe of Nagaland (0.000) and the highest being

Table 2. Hb E frequency distribution in several population groups (Caucasoid origin) of Assam, Northeast India

Sl. No.	Population from Assam	N	HbAE %	HbEE %	HbE frequency	Source
Linguistic group Indo-European						
34.	Assamese (Lower Assam)	112	15.9	2.8	0.107	Flatz et al. 1972
35.	Assamese (Upper Assam)	133	19.5	3.8	0.135	Das et al. 1975
36.	Brahmin	98	10.2	2	0.051	Deka et al. 1988
37.	Kalita	104	19.2	1.9	0.115	Deka et al. 1988
38.	Kaibarta	101	24.8	1	0.133	Deka et al. 1988
39.	Kaibarta	124	20.2	18.5	0.286	Balgir 1991b
40.	Muslim	104	19.2	1	0.101	Deka et al. 1988
41.	Muslim (Garia)	205	13.2	0.5	0.070	Ahmed Das 1994
42.	Muslim (Maria)	155	23.8	3.8	0.158	Ahmed Das 1994
43.	Mixed Indid group	324	17.9	3.4	0.123	Deka et al. 1988
44.	Sikh (Assamese)	15	20.0	20.0	0.300	Balgir 1995
45.	Sikh (Assamese)	107	32.71	5.6	0.209	Sharma and Mahanta 2013

Table 3. Hb E frequency distribution in several population groups (Mongoloid origin) of Arunachal Pradesh, Northeast India

Sl. No.	Population	N	HbAE %	HbEE %	HbE frequency	Source
Linguistic group Tibeto-Burman						
46.	Adi	35	11.4	0	0.057	Balgir and Dutta 1990
47.	Adi (Gallong)	113	25.7	5.3	0.181	Saha 1990
48.	Adi (Gallong)	108	35.2	3.7	0.210	Urade 2014
49.	Adi (Minyong)	42	16.7	0	0.083	Saha1990
50.	Adi (others)	60	16.7	1.6	0.099	Saha1990
51.	Apatani	29	10.3	0	0.052	Balgir and Dutta 1990
52.	Apatani	79	11.4	0	0.057	Saha 1990
53.	Nishi	117	12.0	0	0.060	Balgir and Dutta 1990
54.	Nishi	216	13.0	0.9	0.074	Saha 1990
55.	Other mixed tribes	22	9.1	4.5	0.090	Balgir and Dutta 1990
56.	Other mixed tribes	58	10.3	1.7	0.068	Saha 1990

Table 4. Hb E frequency distribution in several population groups (Caucasoid origin and Mongoloid Origin) of Manipur, Northeast India

Sl. No.	Population	N	HbAE %	HbEE %	HbE frequency	Source
			Caucasoid origin			
Linguistic group Indo European						
57.	Brahmin	108	5.6	0	0.028	Singh et al. 1986
			Mongoloid origin			
Linguistic group Tibeto-Burman						
58.	Ghagte	117	5.9	0	0.030	Singh and Singh 2008
59.	Kabui	162	7.4	0	0.037	Singh 2008
60.	Hill Kabui	270	6.3	0.3	0.035	Singh et al. 2010
61.	Khurkhul (Section of Meitei)	123	15.4	0.8	0.085	Singh and Singh 2008
62.	Meitei	203	11.3	1.4	0.071	Chakravarti and Roy 1979
63.	Meitei	104	18.3	1.0	0.101	Singh et al. 1986
64.	Meitei	626	15.81	1.92	0.101	Singh et al. 2010
65.	Muslim	136	11.7	0	0.059	Singh and Singh 2009
66.	Ningthoukhong	122	9.02	0	0.045	Singh and Singh 2009
67.	Phayengs (Section of Meitei)	104	31.7	6.7	0.226	Singh and Singh 2008
68.	Thadou	115	6.9	0	0.035	Singh and Singh 2009
69.	Koireng	174	5.75	0	0.029	Singh et al. 2010
70.	Simte	164	2.44	0	0.012	Singh et al. 2010

found among the Bodo Kacharis (0.640) of Assam. Within the Caucasoid group the highest frequency of HbE gene being detected among the Assamese Sikhs of Assam (0.300) and lowest being detected among the Brahmins (0.028) of Manipur.

It was suggested that population genetics of HbE in Assam differs from that of Southeast Asia (Deka et al. 1988). In Southeast Asia HbE polymorphism is maintained by heterozygote advantage through protection against malaria (Flatz, 1967) and there was evidence for a reduced fertility in HbE homozygote females (Flatz et al. 1965; Hofliger 1971). A study among the Kachari population of Assam (Deka 1981), where falciparum malaria was highly prevalent till the

Table 5. Hb E frequency distribution in several population groups (Mongoloid origin) of Meghalaya, Northeast India

Sl. No.	Population	N	HbAE %	HbEE %	HbE frequency	Source
Linguistic group Austro-Asiatic						
71.	Khasi (from Shillong)	80	38.8	2.5	0.219	Das et al. 1971
72.	Khasi (Shillong)	302	–	–	0.008	Das and Sengupta 2011
73.	Khasi (from Shillong)	120	36.4	4.29	0.225	Flatz et al. 1972
74.	Khasi (from Cherrapunji)	157	4.5	0	0.022	Saha 1990
Linguistic group Tibeto-Burman						
75.	Mixed Bodo	24	16.8	29.1	0.375	Saha 1990

Table 6. Hb E frequency distribution in several population groups (Mongoloid origin) of Nagaland, Northeast India

Sl. No.	Population group	N	HbAE %	HbEE %	HbE frequency	Source
Linguistic group Tibeto-Burman						
76.	Rangma Naga	148	1.4	0	0.007	Saha 1990
77.	Urban Naga	65	3.1	0	0.015	Saha and Tay 1990
78.	Rural Naga	83	0	0	0.000	Saha and Tay 1990
79.	Hmar	81	2.4	0	0.012	Saha and Tay 1990
80.	Naga	44	6.8	0	0.035	Balgir 1991a

Table 7. Hb E frequency distribution in several population groups (Mongoloid origin) of Tripura, Northeast India

Sl. No.	Population group	N	HbAE %	HbEE %	HbE frequency	Source
Linguistic group Tibeto-Burman						
81.	Chakma	162	51.8	9.9	0.358	Das et al. 2002
82.	Darlong	57	49.1	26.3	0.509	Das et al. 2002
83.	Deb barman	104	49	16.3	0.409	Das et al. 2002
84.	Halam	60	50	18.3	0.433	Das et al. 2002
85.	Jamatia	65	38.5	13.8	0.331	Das et al. 2002
86.	Marek	64	50	31.2	0.562	Das et al. 2002
87.	Mog	74	41.9	5.4	0.263	Das et al. 2002
88.	Morasingh	20	0	15	0.150	Das et al. 2002
89.	Noatia	27	11.1	14.8	0.204	Das et al. 2002
90.	Riang	48	50	20.8	0.458	Das et al. 2002
91.	Tripuri	89	53.9	12.3	0.416	Das et al. 2002
92.	Uchai	70	60	21.4	0.514	Das et al. 2002
93.	Mixed tribes	204	41.5	15.6	0.365	De et al.1997

beginning of control measures in 1950s, demonstrated no decrease in reproductive fitness of HbE homozygotes. Deka et al. (1988) suggested that this might be because of the fact that high frequency of HbE in the Tibeto-Burman of Assam was connected with homozygote advantage. On the other hand Balgir (1992) also did not find any significant variation in the reproductive performance of normal and abnormal hemoglobin bearers among the Ahom population of Assam who were suggested to be related to the Austro-Asiatic population. Deka (1981) once suggested that 'E gene is a neutral allele' among the Tibeto-Burman populations of Assam. Therefore Das et al. (1980) suggested that the HbE polymorphism in Assam is of transient nature as HbE allele tends to replace both HbT and HbA. But deviation of the trend has been observed when Das and Sengupta (2013) found that HbE induced anaemia is the determining factor of increased spontaneous abortion and infant mortality among the Ahom population thereby controlling much of the selection pressure on this community upto infant stage. Till date the research outcomes suggest various selection opportunities at this particular locus within the broad sphere of population variation. Therefore

further study in this direction may give more insight and opportunity to explore other dimensions.

Origin and spread of Hemoglobin E

It is very difficult to assert the place of origin of hemoglobin E mutation with possible explanation because of the association of its multiple haplotypes with different β-globin frameworks. And it is also difficult to assess the possible explanation of such a high frequency of HbE in Northeast India than the other Southeast Asian countries. Once it was suggested that the mutation on HbE occurred independently in each haplotype, thus associating it with multiple origin of HbE genotypes. It was proposed that the mutation occurred twice in Southeast Asia (Antonarakis et al. 1982; Fucharoen et al. 1990). As per Antonarakis et al. (1982), the Southeast Asian population possess β^E mutation in two β-gene frameworks, i.e. 2 and 3, with three different haplotypes namely haplotype a (-+-+++-), haplotype b (+----+-) and haplotype c (-+-++-+). They suggested that the less common haplotype b (framework 2) might have been generated from common haplotype a (framework 2) by meiotic crossing over between δ and β globin gene, but haplotype c (framework 3) represented an independent origin of β^E gene. Since these two frameworks differ at positions, 70 nucleotides to the 5′ side of the β^E mutation and 382 nucleotides to the 3′ side of it, their data suggested the existence of atleast two independent origins of the β^E mutation in Southeast Asia. As per their findings hemoglobin associated haplotype 27-2 is the most common in Southeast Asia (Thailand) and the presence of the same haplotype among the Kachari population of Northeast India suggests single origin of HbE in Thailand and Assam (Hundrieser et al. 1988). Deka et al. (1988) once suggested that in case of multiple mutational events, a second mutant might have its origin in the Tibeto-Burman population of Assam. A study (Das et al. 2000) among the tribal population from Tripura of Tibeto-Burman linguistic affiliation suggested that all the mutations observed were linked to framework 2 and also found that type-2 haplotype (5′+++β^E-3′) was most common among them (19 out of 26 chromosomes). In another study in Tripura similar result was also reported by Sil (2008) strengthening the proposition of common origin of HbE gene in populations of Southeast Asia, Assam and Tripura. Thus a separate mutational event among the Tibeto Burman population cannot be asserted with the present state of knowledge. Exploration of HbE mutation in other Tibeto-Burman populations of Northeast India may give further insight to come to a firm conclusion.

In another study (Kazazian et al. 1984) a separate hemoglobin E mutation in two German families (one of Czech extraction and the other of Northern European ancestry) was observed to be associated with 41-1 and 33-2 haplotypes not observed in Southeast Asia. This finding further supported the hypothesis that framework-1 associated HbE gene was a separate mutation and there is nothing to do with this mutation in Northeast India.

A clarification related to the high frequency of HbE in different frameworks in Northeast India might be explained in terms of the occurrence of single mutation as well as single origin

of HbE mutation in Southeast Asia. In due course of time the single mutational genotype might have extended to multiple haplotypes through the recombination '*hot spot*' region by crossing over (Chakraborty et al. 1984; Das and Talukdar 2001). If normal alleles of β-globin are found on multiple haplotype backgrounds then existence of mutant allele in the haplotypes of same framework can only be comprehended through crossing over (Fukumaki and Fuchareon 1991; Fullerton 1996). However explanation of this conjuncture cannot be perceived while we see the simultaneous occurrence of mutation at multiple β-globin frameworks. At this point the third most reasonable suggestion proposed by Das and Talukdar (2001) is about inter-allelic gene conversion. This particular event suggests non-reciprocal transfer of DNA sequences from one chromosome to another by which a mutant allele induces a normal allele to convert into a mutant allele (Shiokawa et al. 1989; Starck et al. 1990). The existence of a mutation on different β-globin frameworks can be explained by an event of interallelic gene conversion also (Fukumaki and Fucharoen 1991; Papadakis and Patrinos 1999). In a study among the Thai population (Ohashi et al. 2004) four major haplotypes (H1-H4) were found and H1 haplotype was appeared to have arisen from the H2 haplotype by a single mutation. On the basis of the pattern of extended linkage disequilibrium they found that β-globin gene cluster contain a recombination hotspot region from position 1663110 to 1665044 of the NT_028310.8 and there is an effect of natural selection on the pattern of linkage disequilibrium. Their study also contributes to the single origin theory of HbE mutation in Thai population. Therefore, single origin of a deleterious β-globin mutation followed by recombination and interallelic gene conversion through time is the reasonable as well as quite acceptable hypothesis at this time to explain the association of the available mutations with multiple haplotype backgrounds and frameworks (Das and Talukdar 2001). With the help of forward-in-time simulation it has been shown that 95% credibility interval estimated age of the HbE variant was between 1240 and 4440 years which coincides with the estimated period in which *P.falciparum* spread from its African tropical origins to other tropical and subtropical regions in the world (Ohashi et al. 2004). Therefore their data supports a recent origin of HbE along with the spread of *P.falciparum* and a rapid increase in allele frequency.

However with the present knowledge the origin and spread of HbE mutation from Southeast Asia cannot be explained with the help of simple gene diffusion model. HbE is very much prevalent in South-east Asia but its highest frequency is found in the periphery of its distribution i.e. in Assam as well as in the other Northeast Indian states. With the present knowledge it may be assumed that the single mutation on HbE took place in one of the Northeastern states and it diffused to Southeast Asia because of the interethnic relations that were present in the near past at least 3000 to 4000 years ago. In the absence of concrete data the earlier proposed hypothesis of Prof. Flatz and supported by Prof B. M. Das regarding the *'Austro-Asiatic'* linkage with HbE cannot be completely ruled out as opposed to independent mutation of HbE among the Tibeto-Burman population of Northeast India (Deka et al. 1988) or among a Proto-Tibeto-Burman of Southeast Asia (Das 2015). Forward-in-time

simulation of different mutational events can be a better option to draw the attention of various researchers in this respect.

It might be possible that HbE mutation once occurred among one of the Austro-Asiatic population group of Northeast India like that of the Khasis (a Austra-Asiatic group) residing in the foothill region of Meghalaya. The mutation on the hemoglobin loci occurred after they separated from the Mundari population. It might be possible that they separated quite early form the Mundari population and underwent a major demographic event such as common founder effect followed by a bottleneck. The mutation on β globin locus occurred much before agriculture as well as falciparum malaria started spreading. A branched Austro-Asiatic group then migrated to Southeast Asia through Northeastern corridor taking with them the hemoglobin E.

Based on Y-Chromosome O-M95 haplotype data it has been suggested that Mundari population appear to be one of the earliest source of populations from which the Khasi-Khmuic and Mon-Khmer populations have separated and migrated to and settled in Southeast Asia, while another wave of migration occurred much latter from Southeast Asia to Andaman and Nicobar island through Thailand and coastal southern Burma (Kumar et al. 2007). If Indian Austro-Asiatic population would have migrated from Southeast Asia then they should have shown the presence of haplogroup O-M122 in Indian populations as suggested by Kumar et al. (2007). But this is not the case in reality and thus goes against the view point of Kayser et al. (2003) on Austro-Asiatic migration from Southeast Asia to India. However mtDNA markers show a different picture of migration as suggested by Kumar et al. (2006) and Thangaraj et al. (2005). The foundation of M31 and M32 macrohaplogroup of mt DNA in India along with its migration shows some new insight like recent gene flow from Northeast India to Southeast Asia (Barik et al. 2009, Wang et al. 2011). The distribution of O-M95 haplotype is almost parallel to HbE where a high frequency is found in Indian Austro-Asiatic population (54%) than the Southeast Asian Austro-Asiatic population (38%). It is unlikely that the haplotype O-M95 may also have selection relaxation in malarial environment in Northeast India as already suggested for HbE. Highest frequency and highest diversity is the best way to speculate the origin of any particular gene or haplotype in a particular geographical location. In such hypothetical situation the origin of HbE can be established in Northeast Indian population.

The age estimation of fossils of anatomically modern man excavated from East Asia is not older than 40,000 YBP (Wu and Poirier 1995; Jin and Su 2000) which again may imply that earliest possible migration of Austro-Asiatic population to Southeast Asia is very recent phenomena (Kumar et al. 2007). The age estimation of haplogroup O-M95 in Southeast Asia is also suggested to be ~8000 YBP (Kayser et al. 2003) which is almost akin to the period of agricultural expansion. All these data may possibly suggest that during migration the Austro-Asiatic population might have took away HbE mutation to Southeast Asia. While another wave of migration as suggested by Kumar et al. (2007) much later by the Mon-Khmer people from Southeast Asia to Andaman and Nicobar may brought HbE to the this Island. A high frequency of Hb E in Northeast

India, its presence in the migratory route as well as its presence among the population groups of Andaman and Nicobar Islands (Murhekar et al. 2001, Barik and Sarkar 2012–13) may bear the testimony of this proposed hypothesis. If this hypothesis holds true more genetic analysis along the migratory routes of possible Austro-asiatic migration and among the other Mongoloid tribes of Andaman and Nicobar Island can throw light in this particular issue.

Now it may be speculated that HbE originated among the Khasis of Meghalaya. It might also be possible that from the Khasis HbE first diffused to the nearby Garo population (a Tibeto-Burman) population. Then the gene flow occurred among the Kacharis (a Tibeto-Burman group), the earliest inhabitants of Assam and the next neighbour to the Garo population. Due to the selection relaxation in the absence of malaria at high altitude, the frequency of HbE got reduced among the Khasis residing in the hill region in due course of time (0.0 20) as opposed to their plain counterpart (0.222). The Garos and the Kacharis who received the HbE gene from the Khasis got it multiplied and reached a very high frequency in due course of time (Garo, 0.50; Kachari, 0.64). The presence of high frequency of Y-chromosomal haplotype OM95 in the Khasis as well as the Garos (Kumar et al. 2007) suggests that earlier both the two matrilineal tribes had close genetic relationship.

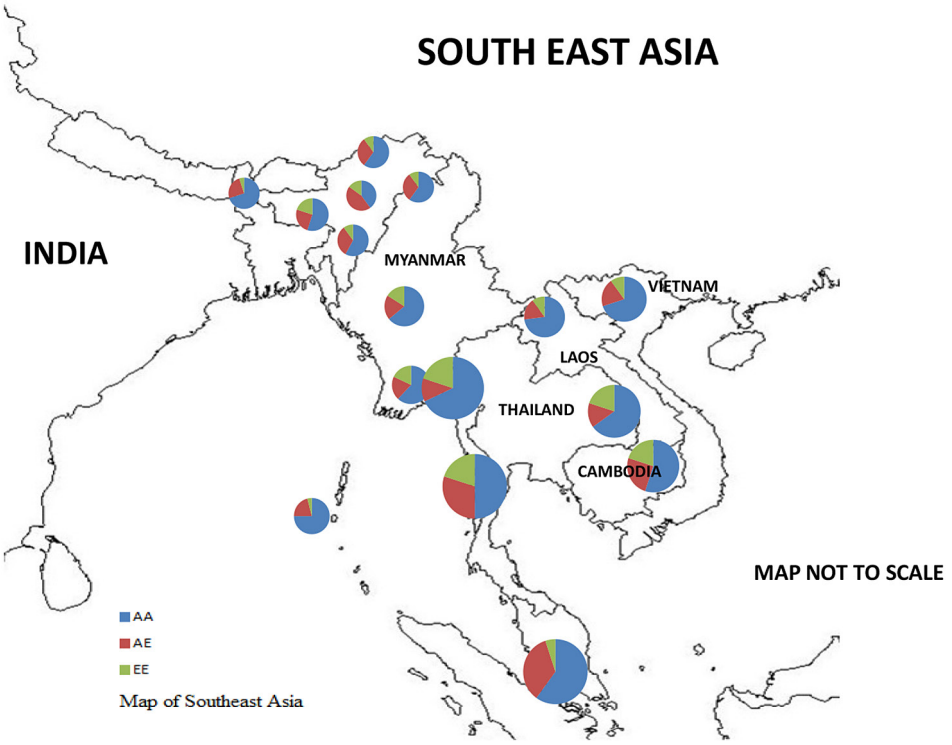

Fig. 2. Hemoglobin E distribution in Southeast Asia (based on average frequency).

Here special mention may be made regarding a study made on the Phayengs of Manipur (Singh et al. 2010) which shows a considerable frequency of HbE gene (0.226). In the absence of clear historical background of Phayengs the authors also speculated that Phayengs have an Austro-Asiatic origin and also pointed out the possibility of matriarchal society among them in near past. Therefore with the present state of knowledge the origin and diffusion of HbE can be associated with Austro-Asiatic population groups. With time the hemoglobin E possibly then diffused to Tibeto-Burman population groups and multiplied to a higher extent probably due to its neutrality in Tibeto-Burman populations in malaria endemic zones. As Deka et al. (1988) once suggested hemoglobin E to be a '*neutral allele*' among the Tibeto-Burman linguistic family. If hemoglobin E is acting as a neutral allele among the Tibeto-Burman population then all the Tibeto-Burman groups of Northeast India including Southeast Asia should indicate high frequency of HbE and researches going on in the present situation shows the same trend. Studies made on Y chromosome haplogroup OM122 and also its derivatives like M-134 (Das and Sengupta 2010) among the Tibeto-Burman population of Northeast India and Southeast Asia show striking similarity of these population groups. In other way the neutrality of the hemoglobin E among all the Tibeto-Burman population and their linkages through molecular analysis can also be established. In this backdrop a high frequency of hemoglobin E among other Tibeto-Burman groups of Northeast India can also be expected.

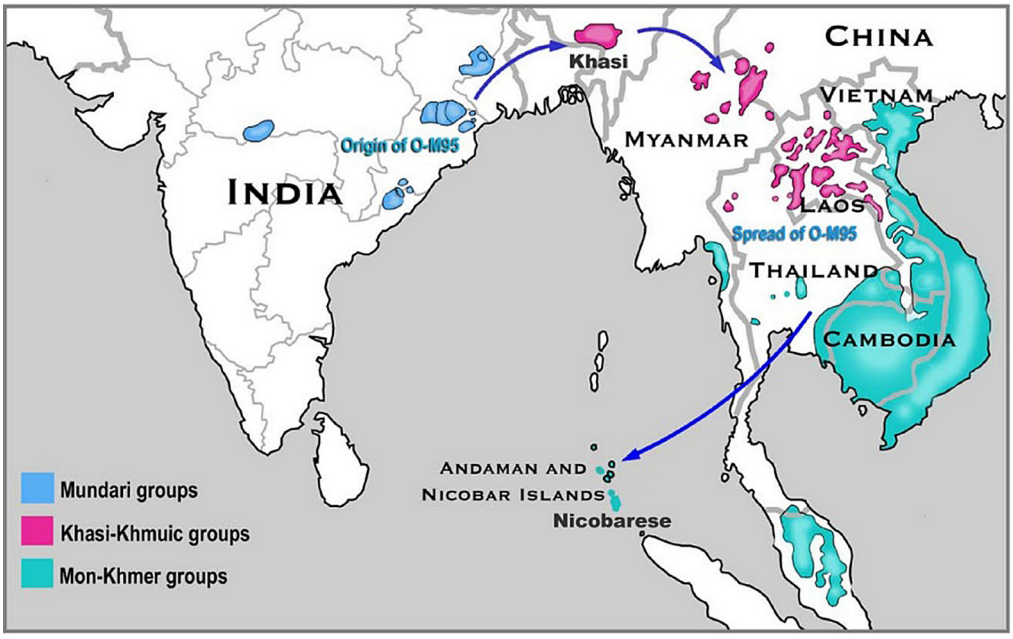

Fig. 3. Routes of migration of different Austro-Asiatic sub-groups (Taken from Kumar et al. 2007).

Hemoglobin E and Malaria

There is no reason to reject the association of hemoglobin E with malaria. It is already established by in vitro analyses that *p. falciparum* grows slowly in homozygous HbE containing RBCs but not in the heterozygous one (Nagel et al. 1981; Vemes et al. 1986). It is shown to be due to the membrane abnormality which includes the differences in membrane rigidity particularly in glycophorin and sialic acid content (Chotivanish 2002). Thus the same relationship of HbE with malaria can be expected in Northeastern population groups also.

It has been found that populations with different ethnic origin show correlation of HbE frequency with mean annual rainfall and mean annual humidity (Bhasin et al. 1994). The reason was anticipated as the factors responsible for breeding of malarial vector. But question rises why there is differences in the frequency of HbE in similar environment with endemic malaria and sometimes there is absence of HbE in the same environment. Notwithstanding the fact that there are other genetic abnormalities like β-thalassemia and G6Pd deficiency that act as protective force in malaria endemicity and are prevalent in various population groups of Northeast India. Therefore we may assume the existence of dynamic interaction within these alleles in such a malarial environment. There may be a reciprocal relationship existing within these genes which may alter the frequency of each other. Therefore while conducting research on any genetic abnormality that can have relationship with malaria hypothesis we can observe the interaction of such alleles with each other. Infact Flatz et al. (1972) once found that the gene frequency product of β^E and β^T is near 3×10^{-3} in all the studied groups in Assam. The same type of relation is also found among the rural population groups of Cambodia (Sanguansermsri et al. 1987).It was found that a rough measure of the selection pressure required to maintain the triallelic Hb polymorphism, is 3.94×10^{-3} and it is comparable with that of the earlier study already made in Northeast India.

It might be possible that this type of reciprocal relationship exist between other genetic polymorphisms of blood. Recent studies also have found a reciprocal relationship between the presence of HbE and G6PD deficiency in different population groups of Assam (Sikdar et al. 2008). In the same context it can be highlighted that the blood group 'O' may provide a protection against malaria. Researchers have found that in O blood group the rosetting is reduced to a significant level and because of that it may give protection against falciparum malaria (Rowe et al. 2007). In Northeast India the frequency of O blood group is also found to be quite high among several population groups (Singh 2011) which may have a protective role in malarial environment. Apart from these, there may be other factors which may have impact on gene frequencies of several allelomorphs. One of such factors might be the practice of inbreeding. Denic and Nicholls (2007) postulated a hypothesis that human inbreeding is the route cause for emergence of some of the most common genetic polymorphisms in humans that are known to protect against malaria. There is also evidence of consanguinity among different population groups of Northeast India. Therefore emergence of various genetic polymorphisms and fixation of the same with the increase of inbreeding cannot be ruled out com-

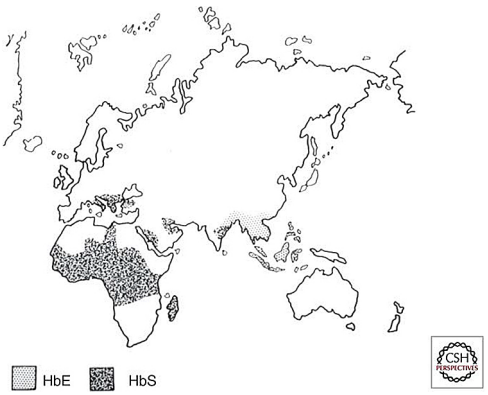

Fig. 4. The world distribution of the origins of Hemoglobin S and Hemoglobin E (From Weatherall and Clegg 2001).

pletely in Northeast India. It may be possible that once the population groups of Northeast India went through the catastrophes of malaria with a concomitant increase of inbreeding and increase in the selective polymorphism. Similarly in the aftermath of potato famine in Ireland and cholera epidemic in Costa Rica in the mid 19th century, an abrupt increase in the rate of consanguineous marriage was also reported (Denic and Nicholls 2007). In the same context Singh et al. (2010) also reported high rate of village endogamy among the Pheyeng population of Manipur together with a high frequency of HbE. An increase in HbE among the Totos of Assam-West Bengal (from 0.099 in 1962 to 0.438 in 2013) with the high incidence of consanguineous marriages may also supports the present conjecture.

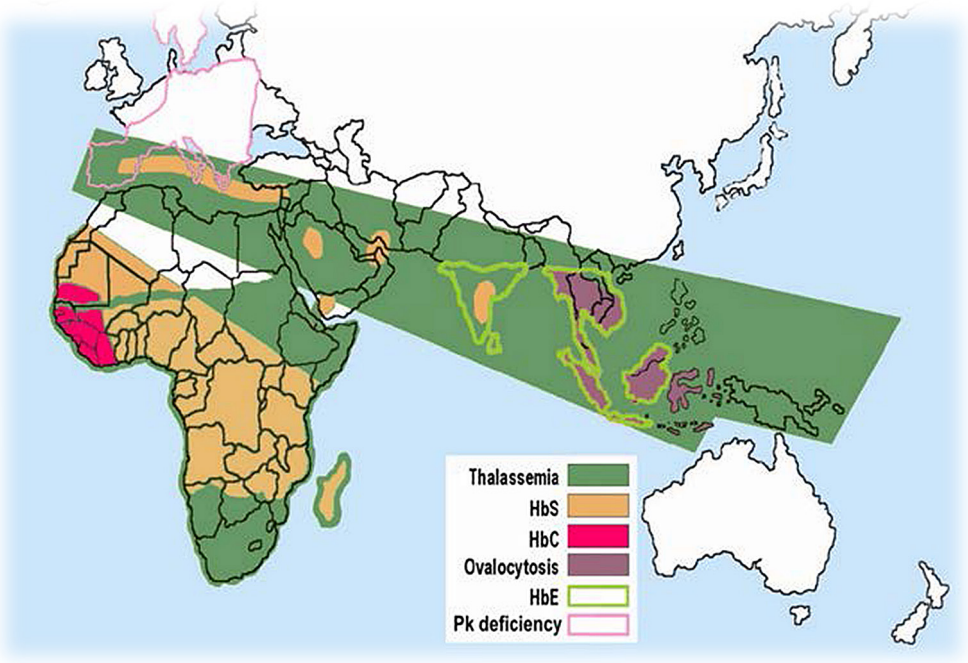

Fig. 5. World distribution of various genetic variants and malaria hypothesis
Source: https://en.wikipedia.org/wiki/Human_genetic_resistance_to_malaria.

Hemoglobin E and Health

Northeast India is undergoing the phase of demographic transition with the improvements in public health measures and hygienic conditions (Hemam and Reddy 1998; Das and Sikdar 2010; Sikdar 2008a; Sikdar 2012a, 2012b). This in turn may increase the genetic load in terms of hemoglobin disorders through reduced level in infant and childhood mortality who will survive until their reproductive period for diagnosis and treatment. Once I hypothesized that together with demographic transition the frequency of the recessive genes like that of hemoglobin E may increase leading to genetic load in a population (Sikdar 2008a) and it became very much implicit with the studies among the Sonowal population of Assam (Barua and Kotal 2008) and Totos of West Bengal (Bhattacharyaa et al. 2013). This type of conjuncture can further be established with the help of restudy of different population groups on different abnormal hemoglobin variants over a particular period of time.

In terms of the frequency of thallasemia same type of demographic changes was graphically illustrated in Cyprus many years before. In this connection it can be relevantly noted that Cyprus underwent this kind of demographic transition shortly after World War II. Although thalassemia was not identified in Cyprus until 1944, by the early 1970's it was estimated that, if no steps were taken to control the disease, in approximately 40 years' time, the blood required to treat thalassaemic children would amount to 78,000 units per annum, 40% of the population would need to be donors, and the total cost to the health services would equal or exceed the island's health budget (Weatherall and Clegg 2001). Hence, although the rate of progression of the epidemiologic and demographic transitions may be slower in countries with a rapidly increasing population, there is no doubt that, given the world distribution of the hemoglobin disorders, these transitions combined with increased population growth will lead to a major increase in the numbers of babies born with one or other hemoglobin disorder over the next half-century (Weatherall 2010). Therefore an increasing concern is also going on about the ill effect of hemoglobin E on the health condition of the individuals around the world and particularly among the population groups in Northeast India.

With respect to hemoglobin E, it is still not clear that whether it has any lethal effect on human health or not. In Northeast India many researchers (Singh et al. 2010) have found that HbE homozygotes live normal life like that of the other polymorphisms of blood groups. In another study in Assam (Das et al. 1979) no significant difference has been found in the hemoglobin percent between the three genotypic variation of hemoglobin (HbAE, HbAA and HbEE) in both the sexes which further demonstrates that HbE homozygotes do not produce any physical abnormality among the people of Northeast India. De et al. (1997) also found that homozygous E individuals of Tripura are not anaemic compared to genotypically normal individuals of the same population.

However deflection of this general trend has been found when the present researcher during one of his fieldwork found that a tribal child of twelve years old with hemoglobin E homozygous condition was undergoing regular blood transfusion from a hospital of nearby town in Assam. Chaliha et al. (2013)

found that there is a significant difference of anemic status among the college going girls of Dibrugarh, Assam with respect to the presence of abnormal HbE either in homozygous or heterozygous condition. The trend was further corroborated in other population groups of Assam (Sikdar et al. 2008). A recent study (Pathak et al. 2014) among the pediatric group showed that there is high frequency of anemia among the children having HbE either in homozogote, heterozygote or compound heterozygote condition. Weakness, aches and pain, splenomegally, hepatosplenomegally, joint pain and stomach pain are also the other morbid conditions among these children.

In this regard attention can be drawn to a study done on the population groups of South Bengal and Tripura (Das et al. 2000) where four types of HbE haplogroup have been found and all of which were linked to framework 2. A comparative account between this haplotype based genotypes and their respective hematological and clinical profiles showed that type 1 homozygotes are more anaemic compared to the homozygotes for type 2 haplotypes. At this stage it is very much prudent to identify the different haplotype variation of HbE while conducting further research on hemoglobin in this part of India to see the role of different haplotypes on the health profile of the various population groups of Northeast India. In Austro-Asiatic populations the HbE is associated with framework 3 (Hundreiseret et al. 1988, Yongvanitet et al. 1989; Fucharoen et al. 1997, 2002) which may have yielded differential survival among the Austro-Asiatic population lowering the HbE frequency among the Austro-Asiatic population in comparison to the Tibeto-Burman population groups over consecutive generation as envisaged in different studies.

There is another condition known as compound heterozygosity of HbE with thallasemia which is very much frequent in Southeast Asia including Northeast India. Hb E/β-thalassaemia results from co-inheritance of a β-thalassaemia allele from one parent and the structural variant hemoglobin E from the other. Hemoglobin E produces structurally abnormal hemoglobin as well as activates a cryptic splice site that result in abnormal messenger RNA (mRNA) processing. In this action the level of normally spliced mRNA, βE, is reduced. A new stop codon is generated and as a result the abnormally spliced mRNA become non functional. Hence, hemoglobin E is synthesized at a reduced rate (Orkin et al. 1982) and behaves like a mild form of β-thalassaemia. The pathophysiology of Hb E/β-thalassaemia is related to many factors including reduced β chain synthesis. It may ultimately result into globin chain imbalance, ineffective erythropoiesis, apoptosis, oxidative damage and shortened red cell survival (Dutta et al. 2006, Pootrakul et al. 2000). In general, it appears that the recognized instability of hemoglobin E is a minor factor in the overall pathophysiology of Hb E/β-thalassaemia, except during inter-current febrile illnesses during which such instability may result in accelerated hemolysis (Jetsrisuparb et al. 2006). There is much more to be done in this particular domain of research and Northeast Indian region offers us prospective issues to be uncovered in due course of time.

Conclusion

The present review on hemoglobin E in Northeast India has been divided into

five headings i.e. peopling of Northeast India, hemoglobin E research in Northeast India, origin and spread of hemoglobin E, hemoglobin E and malaria hypothesis, hemoglobin E and health. The first part describes the ethnic composition of Northeast India along with its linguistic diversity. It offers us the scope to carry out population based screening of hemoglobin E to understand the dynamics of the genetics of hemoglobin E in different population groups of Northeast India which is yet to be conducted in real sense of the term. The second part takes into account the history of research on hemoglobin E in Northeast India and also the studies showing differential frequency distribution of hemoglobin E in different population groups of Northeast India. We can have a look that most of the works on hemoglobin E have been confined to Assam and Manipur thus offering us a scope to extend our dimension of research to other parts of Northeast India. The third part describes the probable origin of HbE among an Austro-asiatic population group with the help of molecular anthropological knowledge and new insight on population migration. The probable correlation of hemoglobin E with malaria has been dealt in the forth section. Here the relation of HbE with malaria hypothesis has also been correlated with the reciprocal relationship of other genetic polymorphism like blood group O, G6PD deficiency etc. The last section described the patho-physiology of hemoglobin E along with other co-inherited conditions like thallasemia. The interlinkages of hemoglobin E with the demographic transition is also talked about in this section which shows continuous increment of genetic load in different population of Northeast India. The attempt to review the studies on hemoglobin E in Northeast India will not only enrich the existing dataset on hemoglobin research but will also try to fill the gap of new perspectives to be undertaken in due course of time.

Conflict of interest

The author declares that there is no conflict of interests regarding this work.

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